# Effectiveness and implementation of influenza vaccination

A non-experimental approach

E. Hak

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# Effectiveness and implementation of influenza vaccination

A non-experimental approach

**Effectiviteit en implementatie van influenzavaccinatie**

Een niet-experimentele benadering
(Met een samenvatting in het Nederlands)

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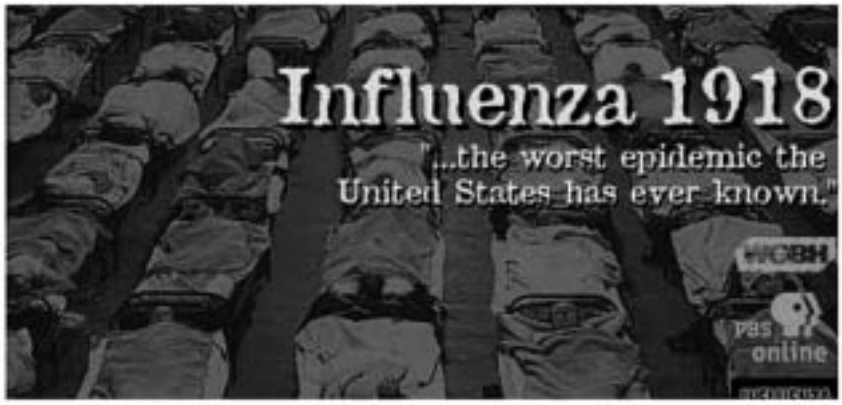
# Contents

CHAPTER I

# Introduction

**Influenza pandemic: the Spanish flu.**




'The world was at war in 1918. Millions of troops were fighting a largely ground struggle in Western Europe. Influenza was first reported in March 1918 from fort Riley, Kansas, United States. The virus appeared to have swept the world in three waves over less than two years' time, gaining virulence with each new assault. Crowding in the military was responsible for high attack rates reported a month later. Forty percent of US Navy personnel became ill. There were 54,000 battle deaths among US forces and 43,000 influenza and pneumonia deaths. By October 1918 its strength was so great that people died with spectacular speed. Influenza led to cyanosis and death from pneumonia within 2 to 3 days of onset. There were even reports of women boarding a New York subway feeling little else than mild fatigue and being found dead when the train stopped 45 minutes later. In New York alone, over 20,000 citizens died. In two months time, 1 in 130 citizens of Philadelphia died from influenza. Disease was reported across Europe in May, in Africa in June and India and China in August. In times of steamships and horses influenza had circled the globe in less than 5 months. Estimates of the total number of deaths worldwide vary from 20 to 40 million leading to social disruption including a shortage of coffins.'

**Photo:** http://www.pbs.org/wgbh/amex/influenza, accessed March 12th, 2001

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# Introduction

**The burden of influenza**

The unique epidemiology of the influenza virus is characterized by winter epidemics of respiratory disease in temperate climates circulating globally with attack rates of 10 to 30 percent. In the United States and the Netherlands, 20,000 cases and 2,000 excess deaths occur during influenza epidemics every year.[1,2] Also, the virus has caused three global pandemics in the 20th century.[3] Pandemics occur once every 30 to 40 years and the pattern is characterized by a start from a single location and global spread along the travel routes. Influenza pandemics are responsible for millions of hospitalizations and deaths worldwide.

The high mutability of its antigens is the key to its ability of the virus to cause annual epidemics and periodic pandemics. Influenza A, categorized into subtypes according to their hemaglutinin (H) and neuraminidase (N) components, and influenza B are the two main types causing human infections. Infection occurs in all age groups, but the infection rates are highest among children, while serious disease and mortality mainly occur among the elderly and those with high-risk medical conditions, regardless of age.[4]

The main transmission route is from person to person by droplet spread containing up to $10^5$ virus particles/ml.[5] The incubation period is short, averaging two days, and people may be infectious before any symptoms appear. Uncomplicated influenza is characterized by sudden onset of fever, headache, cough, myalgia, or other constitutional symptoms.[6] Gastrointestinal symptoms sometimes accompany respiratory symptoms in infants and children. Usually, influenza is self-limiting, lasting 3 to 5 days. By disruption of epithelia of the respiratory tract and decreased mucociliary clearance, it can predispose to complications such as otitis media,[7] exacerbations of underlying lung disease[8] or cardiac disease[9] and viral or secondary bacterial pneumonia[10-12] often needing hospitalization and sometimes fatal.[4] Since the changes in antigenic make-up of the virus are unpredictable,[13] the influenza virus will continue to exact its toll of morbidity and mortality unless preventive and therapeutic measures targeted at those who need them are implemented.

**Prognosis of influenza**

As preventive health care budgets are limited, large-scale measures for the control of influenza should focus on individuals with a high probability of developing complications from it. The available methodology commonly used to study the prognosis of influenza in the community include cohort and case—control studies. In the time before large-scale influenza vaccination was

introduced,[14,15] or when vaccination rates were still relatively low,[16-19] some studies focused on establishing risk factors for serious outcomes such as need for hospitalization for influenza and pneumonia, or deaths from all causes during epidemics. More recent prognostic information has been acquired through non-experimental vaccine effectiveness studies.[20-25] Factors that have consistently been shown to be independently related to increased risk of such outcomes include age (notably infants and young children[18,19] and the elderly[20-25]), underlying disease (e.g. chronic cardiac, pulmonary or metabolic disease; renal dysfunction; hemoglobinopathies or immune-suppression),[4] pregnancy[26] and place of residence during epidemics (nursing home or hospital).[27,28]

**Limitations of current prognostic evidence**

Several potential limitations need to be considered when trying to use currently available prognostic evidence from existing studies in clinical practice. Firstly, the statistical analyses employed in all studies were incomplete —though most used logistic regression analysis techniques to assess the independent associations of potential risk factors with the relevant end point, none extended the analysis by developing a clinical prediction rule to estimate the probability of an individual having that end point.[29] Data on individual absolute risks of complications are, however, essential for development of efficient preventive and therapeutic measures. Secondly, most of these studies were conducted in North-America. In Europe, general practitioners have a pivotal role both in delivering health care and in selection of patients for secondary or tertiary care. The results of the few prognostic studies carried out in European countries[21,25] differ from those from North-America.[14-20,22-24,26] The absence of studies on determinants of endpoints other than the serious complications death or admission to hospital for influenza or pneumonia is another limitation. Some studies, for example, have shown that during influenza epidemics the incidences of exacerbations of chronic pulmonary disease,[12,30-32] deterioration of metabolic control in diabetes[33] or acute cardiac disease[34,35,9] are associated with the incidence of influenza in the community. However, the risk of these complications that is attributable to influenza infection is largely unknown.

**Options for the control of influenza**

The main direct option for reducing the impact of influenza is immunoprophylaxis with conventional inactivated (i.e. killed-virus) vaccine.[4,36] Other options include immunoprophylaxis with intranasally administered cold-adapted live-attenuated influenza virus vaccines,[7,37] and use of antiviral drugs such as amantadine and rimantadine, or neuraminidase inhibitors such as zanamivir and oseltamivir. The first antiviral drugs are effective against

influenza A only and can cause considerable adverse effects.[38] Treatment with zanamivir[39,40] or oseltamivir[41] reduces the course of influenza infection by 1 to 1.5 days. Preventive use of these latter neuraminidase inhibitors reduces the occurrence of influenza illness by 30 up to 89 percent, [42-44] similar effects as the conventional influenza vaccination in healthy persons.[45] Although it might be expected that prophylactic use of neuraminidase inhibitors increases protectiveness against influenza when given simultaneously with influenza vaccination, no effectiveness studies have been carried out among the current vaccine target population. Another major constraint on using these drugs is the difficulty of making an accurate diagnosis of influenza in time to be of value.[36] In the Netherlands, these drugs are therefore not recommended for large-scale use for either prophylaxis or treatment.

**Conventional inactivated influenza vaccine**

According to the recommendations of the World Health Organization, the conventional vaccine contains two types A strains and one type B strain forecast to be the most likely to circulate in the coming winter.[4] The current vaccine is made from virus grown on embryonated eggs. After ultra-centrifugation, virus particles are highly purified and then killed by formaldehyde. Virus mutation by antigenic drift and shift means that a new vaccine needs to be developed each year. The essential data to predict likely new strains are produced by a global network of surveillance laboratories.[46] The development process takes up to six months which is short enough to prepare for regular epidemics, but too long for response to a potential pandemic.[47] Therefore, other vaccine production processes are being developed to enable a higher production capacity.

**Influenza vaccine efficacy and effectiveness**

In general, epidemiological studies on the impact of vaccines distinguish two measures: vaccine efficacy and vaccine effectiveness.[48] Vaccine efficacy is commonly assessed in pre-marketing randomized double-blind placebo-controlled clinical trials. The most frequently used clinical endpoints in such trials include post-vaccination protective antibody titers as a measure of indirect protection and influenza infection rates as a measure of direct protection. Study populations include healthy people and sometimes patients in a limited range of high-risk categories. In influenza vaccine trials, most vaccinated children and young adults developed protective antibody titers against influenza with strains similar to vaccine components.[45,49,50] Some studies suggest that elderly persons[51] and patients with certain chronic diseases[52,53] (the most important subgroup to target for vaccination) may develop lower titers. Only one randomized placebo-controlled trial has been conducted to establish clinical direct effects of vaccination among healthy elderly people.[54] In this Dutch

study by Govaert et al. the vaccine appeared to reduce the incidence of serologically confirmed influenza by 50%.

For overall protective clinical effect in routine clinical practice calculated from post-marketing studies the term 'vaccine effectiveness' is often used. Influenza vaccine effectiveness is the result of both the vaccine's direct effect, which refers to the ability of the vaccine to protect the individual against clinical influenza infection and its complications, and the indirect effect, which refers to reduction of the spread of influenza in the population. This latter effect is one of the reasons to vaccinate persons in closed communities such as nursing homes,[27] health care institutions[28] and day-care for children.[55] Vaccine effectiveness can be estimated using post-marketing study designs including pragmatic randomized controlled trials, cohort and case—control studies incorporating clinical end points relevant to the individual patient. In cohort studies, vaccinees and non-vaccinees are followed up retrospectively or prospectively and incidences of complications of influenza in both exposure groups are compared. The common measure of association is the incidence rate ratio which may be considered as a relative risk (RR). In case—control studies, frequency of exposure, i.e. vaccine use, in cases and controls (randomly sampled from the study base) is compared. In these case—control studies, the common measure of association is the odds ratio (OR) or, in case of a matched design, the ratio of discordant pairs. In general, vaccine effectiveness in percent is given by 1—RR*100 in trials and cohort studies or 1—OR*100 in case—control studies.[5]

In contrast to the scarcity of large randomized placebo-controlled trials with clinically relevant endpoints, there are many published non-experimental studies on influenza vaccine effectiveness. Gross et al. have summarized the results of 20 such studies carried out among the elderly.[56] The pooled estimates of vaccine effectiveness were 56 percent (95 percent confidence interval 39 to 68 percent) for preventing respiratory illness, 53 percent (35 to 66 percent) for preventing pneumonia, 50 percent (28 to 65 percent) for preventing hospitalization and 68 percent (56 to 76 percent) in preventing death. One of the key studies on the vaccine's effectiveness on severe end points was a serial prospective cohort study among the elderly by Nichol and colleagues.[20] In this study, more than 25,000 elderly non-institutionalized seniors were followed up using medical databases during three consecutive influenza periods. The overall vaccine effectiveness in reducing the incidence rates of death or hospitalization for pneumonia or influenza appeared to be between 48 and 57 percent. In another earlier case—control study, Fedson and colleagues observed reductions in hospitalizations for pneumonia or influenza of between 29 and 32 percent,

and reductions in mortality from all causes of between 27 and 30 percent among persons aged 45 years or older.[23] Another key study published by Ahmed and colleagues estimated a 41 percent reduction in mortality from all causes in a case—control study among subjects aged 16 years or older, mostly elderly.[57] Most subsequent studies among the elderly confirmed the vaccine's effectiveness in reducing serious complications such as need for hospitalization for influenza or pneumonia, or death with estimates varying from 40 to 60 percent.[22,25,58]

**Limitations of current evidence for influenza vaccine effectiveness**

The various limitations in validity and applicability of the results of the existing studies might, however, have led to sub-optimal clinical guidelines for influenza control. One of the major drawbacks of non-experimental evaluation studies of drugs is the potential for 'confounding by indication'.[59] Vaccinees and non-vaccinees are not randomly selected and in practice these groups differ with regard to average prognoses. In health care systems with a strong primary care component, vaccinees tend to have more risk factors than non-vaccinees. Unadjusted effectiveness estimates might therefore obscure a potential positive effect of the vaccine or at least underestimate its true protectiveness. Although most studies have controlled for the presence of these confounding factors by applying regression techniques, other techniques in the design or data-analytical phase of the study such as restriction of the study population or the design of a quasi-experiment using propensity scores[60] have not often been used for further control for residual confounding.

Other validity issues, particularly with case—control studies, include potential information bias and selection bias.[61] The first refers to differing information on cases and controls regarding the presence of vaccination or prognostic variables. The use of medical databases greatly reduces such information bias and most large-scale studies have therefore collected data by review of computerized patient records. Selection bias may be present when cases or non-cases are selected on the basis of their vaccination status. To prevent differential selection of outcomes for vaccinees and non-vaccinees, the case definition should be strictly applied. Therefore, most studies use death or hospitalization for influenza or pneumonia as the main endpoints. However, potential invalidity of study results remains a concern and authors should carefully discuss potential sources of bias in their study.

Finally, most vaccine effectiveness studies were conducted among the elderly or institutionalized populations. Only few were carried out among children with chronic high-risk disease and they were small, and covered one influenza season

only. In studies including infants and children, the vaccine reduced the occurrence of episodes of otitis media by 40 percent[7,62,63] and the number of febrile influenza episodes among young asthmatics by 49 percent.[64] Among the large group of patients with high-risk disease of working-age no such clinical benefits from influenza vaccination have been reported so far and studies are therefore needed.

**Adverse effects of influenza vaccination**

The literature on the potential adverse effects of the vaccine is vast. Local reactions such as soreness at the site of vaccination usually lasting about two days occur in 10 to 64 percent of patients.[4,36] Severe systemic reactions may occur in patients who are hypersensitive to egg-allergens, so egg hypersensitivity is a contra-indication to conventional influenza vaccination, though in practice it is very rare. Although an association with Guillain-Barré syndrome has been put forward,[65,66] this risk, if present, is as low as one in a million. In all, the conventional influenza vaccine may be considered safe, even in combination with routine child vaccinations or pneumococcal vaccines.[67]

**Implementation of a population-based influenza vaccination program and coverage**

Epidemiological studies among the elderly and few among high-risk children have demonstrated a high impact of influenza and clinical benefits of annual influenza vaccination. Further knowledge on the barriers to implement an immunization program is required to be able to effectively control its public health burden.[68] To develop and maintain an effective preventive program, clear clinical guidelines for care-givers are needed.[69] As a first step, the Dutch Health Council followed by the Dutch College of General Practitioners summarized evidence for the need for control of influenza by annual immunization against influenza.[70] Furthermore, numerous studies on the acceptance of influenza vaccination among patients have shown that non-compliance with annual vaccination programs is mainly associated with lack of personal recommendation by a physician, lack of awareness of the risks of influenza and fear of adverse effects.[71-74] Educational programs are therefore needed to reach and convince both physicians and high-risk subjects of the health benefits of vaccination. Finally, logistical problems inherent in vaccine supplies should be minimized, and selection of high-risk people for vaccination should be facilitated. In the Netherlands, general practitioners play a key role in the health care delivery. Almost all Dutch inhabitants are registered with a GP. Also, more than 80% of Dutch GPs record all patient contacts in computerized medical records. Facilities for computerized selection of high-risk patients and administration of the preventive services are therefore easily available. GPs are

thus in a unique position to target preventive care, especially immunization programs, to those who need it. A small-scale experimental study carried out in 1993 demonstrated that an educational program aiming at GPs to set up a step-wise influenza vaccination program was successful in increasing influenza vaccination coverage among their vaccine target population.[75] Based on this study and other educational studies,[69,76] the Dutch Ministry of Health, Sports and Welfare decided in 1995 to provide financial support for a nationwide preventive program called 'Tailor-made prevention' to educate GPs and facilitate preventive tasks including influenza vaccination.

## Outline of this thesis

The three parts of this thesis aim at filling some essential gaps in our scientific knowledge on (I) prognosis of influenza, (II) vaccine effectiveness in high-risk subgroups and (III) effects of implementing a nationwide primary care based influenza immunization program.

**Part I. Prognosis of influenza**
In chapter 2 we aim at identifying prognostic factors for influenza-associated death and/or admission to hospital in Dutch adults with high-risk medical conditions who require influenza vaccination. We specifically address the potential modification by age of associations of patient factors with the end points among patients of working-age as compared with the elderly. In chapter 3, we describe how a large-scale influenza vaccination monitoring and evaluation program covering non-institutionalized elderly people in three geographically disparate Health Maintenance Organizations (HMOs) across the United States enabled us to develop and validate a clinical prediction rule for the need for hospitalizations for influenza or pneumonia, or death from all causes.

**Part II. Clinical effectiveness of influenza vaccination**
In chapter 4 we elaborate on 'confounding by indication' in non-experimental evaluation of influenza vaccination as one of the major methodological problems of using cohort and case—control study designs. We also suggest some tools to reduce the impact of such bias and illustrate the effects of some of these options with part of the data from the study described in chapter 6. In chapter 5 we describe a serial retrospective cohort study aimed at establishing the potential clinical benefits of annual influenza vaccination among children with asthma. This study covered the 1995/96 and 1996/97 influenza A epidemics.

In chapter 6 we present the results of a prospective cohort study among patients with asthma or COPD aged 18 years or over during the 1995/96 influenza A epidemic. In this study we determined the occurrence of influenza-associated morbidity and mortality and clinical benefits of influenza vaccination with particular emphasis on the potential modification of vaccine effects by age (18 to 64 years versus ≥65 years). In chapter 7 we report our serial prospective nested case—control study among asthma and COPD patients of working-age to determine the occurrence of influenza-associated respiratory and cardiac morbidity and mortality, and the effect of influenza vaccination in reducing these complications. Study subjects were followed during the 1998/99 influenza type B epidemic and the 1999/2000 influenza A epidemic. In chapter 8 we assess the influence of various high-risk medical conditions on the effectiveness of influenza vaccination among non-institutionalized elderly members of three large HMOs. The observations of this prospective cohort study covered the 1996/97 and 1997/98 influenza A epidemics in the United States.

**Part III. Implementation of influenza vaccination**

In chapter 9 we report the collection of baseline data from a random sample of Dutch GPs before the nationwide introduction of the 'Tailor-made prevention' program. In this study we assessed independent characteristics predicting a high overall immunization rate. In chapter 10 we evaluate whether the introduction of a computerized influenza prevention module in a general practitioner information system facilitates the various logistical aspects of the influenza immunization program in Dutch general practice. In chapter 11 we present data of an uncontrolled before-and-after trial on the effects of a coordinated nationwide program called 'Tailor-made prevention' that aimed at improving influenza immunization practice in the Netherlands.

The thesis ends with a general discussion of our findings with respect to implications for future control of influenza-related morbidity and mortality. In addition, this last chapter provides suggestions for further study into various aspects of this major and continuing public health issue.

**Essential issues dealth with in this thesis**

| What is already known? | What is largely unknown? | Chapter |
|---|---|---|
| *Part I. Prognosis of influenza* | | |
| Influenza affects persons of all ages | The incidence of complications other than hospitalization for influenza or pneumonia, or death | 5, 6, 7 |
| Infection rates are highest among children | The occurrence of influenza-associated morbidity and mortality in children and patients with high-risk conditions of working-age | 5, 6, 7 |
| Complications of influenza infection include lower respiratory tract infections, acute cardiac disease, diabetes events and death | The extent to which prognostic factors are associated with rare influenza complications and whether age modifies the associations | 2, 3 |
| Patients with certain medical conditions, elderly, pregnant women and people in institutions are at high risk for complications of influenza | The absolute risk of an individual's developing complications from influenza and whether a clinically useful prediction rule can be developed | 3 |
| *Part II. Clinical effectiveness of conventional influenza vaccination* | | |
| Most evidence is acquired through non-experimental studies. | Whether 'confounding by indication' can be adequately prevented or limited | 4 |
| Influenza vaccination reduces respiratory illness, influenza and pneumonia hospitalizations and death in the elderly by 30% to 50% | The reduction of influenza-associated respiratory morbidity in high-risk children and patients of working-age | 5, 6, 7 |
| Influenza vaccination might lead to lower protective antibodies in elderly persons and persons with high-risk medical conditions | Whether specific high-risk medical conditions or age influence the vaccine's efficacy | 6, 8 |
| *Part III. Implementation of influenza vaccination* | | |
| Clinical guidelines are essential for effective preventive care | To what extent Dutch GPs follow the influenza vaccination guidelines | 9 |
| Personal reminders by physicians increase the acceptability of vaccination by the vaccine target group | Which practice and organizational characteristics in Dutch general practice predict optimal immunization rates | 9 |
| Immunization practice might efficiently be implemented in primary care | Whether computerized facilitation modules effectively increase vaccine coverage | 10 |
| Educational efforts should focus on misconceptions about influenza risks and vaccine effectiveness | Whether a large-scale multi-faceted educational program could succeed in improving immunization practice in primary care | 11 |

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# Part I

## Prognosis of influenza

CHAPTER 2

# Prognostic factors for influenza-associated hospitalization and death during an epidemic

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**Prognostic factors for influenza-associated hospitalization and death during an epidemic**

To predict which patients with current high-risk disease in the community may benefit most from additional preventive or therapeutic measures for influenza, we determined prognostic factors for influenza-associated hospitalization and death in a general practice-based case-control study among this segment of the vaccine target population with high influenza vaccination rates. In 103 general practices followed during the 1996/97 influenza epidemic, cases were either hospitalized or died due to influenza, bronchitis, pneumonia, diabetes, heart failure or myocardial infarction. Age- and gender-matched controls were randomly sampled from the remaining cohort. Information was collected by review of patient records. In total, 119 cases and 196 matched controls were included. Of the cases, 34%, 25% and 4% were hospitalized for acute pulmonary and cardiac disease and diabetes, respectively, and 37% died. Multivariate conditional logistic regression analysis revealed that presence of chronic obstructive pulmonary disease, heart failure, previous hospitalization, high GP visiting rate and polypharmacy were independent prognostic factors. Several non-modifiable determinants can be used to facilitate targeting additional preventive or therapeutic measures at the most vulnerable segment of the vaccine target group.

**Key-words:** influenza, vaccine, prevention, general practice, effectiveness, epidemiology

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Influenza continues to cause considerable morbidity and is considered one of the world's major killer diseases.[1,2] Recently, much attention has been given to a potentially upcoming influenza pandemic that may result in large numbers of casualties, especially among those with high-risk medical conditions.[3] To reduce the health and economical burden of influenza infection, use of inactivated vaccines by vulnerable patient groups is a major topic in preventive health care policy.[4] However, although influenza vaccination rates are reaching high levels, immunization does not confer full protection.[5,6]

In order to increase the impact of additional clinical measures against influenza or its sequelae such as the use of neuraminidase inhibitors or pneumococcal vaccines, knowledge about patients most likely developing complications of influenza is indispensable. Physicians should be able to routinely reach patients at highest risk, even if immunized against influenza, to direct other preventive or therapeutic regimens.[7] Additional studies with the primary objective to assess clinical determinants of an increased risk of serious influenza-associated

complications among the largest segment of the vaccine target group, outpatients with current high-risk medical conditions, are therefore needed.

As part of an ongoing study to assess the effectiveness of a nation-wide collaborative primary care program to enhance influenza vaccine uptake in the Netherlands,[8] we conducted a case-control study to establish prognostic indicators for influenza-associated hospitalization and death among adult patients with high-risk chronic disease given current immunization rates.

## Methods

**Setting and design**

Our study is part of an evaluation of the nation-wide intervention program 'Tailor-made prevention' that was implemented between 1995 and 1997 to foster population-based prevention of influenza and cervical cancer in Dutch general practice.[8,9] A sample of 56 computerized general practice (GP) centers using the GP information system ELIAS (SMS Cendata, Wageningen) involving 103 GPs, participated in the present study. ELIAS has been developed to support large-scale epidemiological studies in primary care by facilities such as integration of coded information on disease status, reasons for encounter and medical prescriptions in the computerized patient records, and search modules to enable storage of data in a study database.[10] Participating GP centers were spread all over the Netherlands and relevant anonymous data were supplied by GPs to the data-management center of the Julius Center, University Medical Center Utrecht.

We designed a case-control study nested in the primary care centers' cohort of adult outpatients with high-risk chronic medical conditions requiring annual influenza vaccination according to Dutch immunization guidelines.[11] In October 1996, patients with potential current high-risk disease who were eligible for inclusion into our study were selected by means of a computerized influenza prevention software module. Details on the module's stepwise selection procedures have been described elsewhere.[7] In short, patients were identified using their date of birth and presence of medical disorders was identified on the basis of relevant entries of ICPC diagnosis codes, ATC medical drug codes and tags indicating chronic disease in computerized patient records. Conditions were grouped as pulmonary disease (chronic obstructive pulmonary disease [COPD], asthma, lung cancer or other pulmonary disease), heart disease (heart failure, myocardial infarction, valvular heart disease, angina,

and cardiomyopathy), diabetes mellitus, renal disease and other diseases (including malignant disorders, neurological disease). In November 1996, we identified a cohort of 18,163 patients with registered codes indicating potential high-risk disease among the total vaccine target population including healthy elderly (n=32,425 persons).

**Identification of hospitalized and fatal cases during 1996/97 influenza epidemic**
The epidemic period was defined from 23 December 1996 to 16 February 1997 as influenza peak activity was observed between these dates.[12] Questionnaires were sent fortnightly to participating GPs to identify hospitalized or deceased patients. Study subjects qualified as a case if they were admitted to the hospital during the epidemic with a primary diagnosis of an acute episode of influenza, bronchitis, exacerbation of underlying lung disease, pneumonia, diabetes dysregulation, congestive heart failure or myocardial infarction or if they died from these causes. After the epidemic the case definition was verified by the participating GPs. If a specialist certification letter was present at the GP's office, a photocopy was obtained.

Our objective was to establish prognostic factors among the segment of the adult vaccine target outpatient population with current high-risk disease, regardless of age. To ensure the presence of current high-risk disease at inception of the cohort in November 1996, potential cases had to be excluded from the study population if no registration of GP contact for their chronic condition in the preceding 24 months was present (so-called 'inactive patients') or if they moved out of the general practice or died before the epidemic ('ghost patients'). Verification of current disease and specific diagnosis at baseline until the beginning of the epidemic was made retrospectively by the GPs in April 1997. Surveillance of complications during the epidemic resulted in 202 potential cases identified and screened for eligibility. We excluded 37 patients without chronic medical conditions at baseline or lack of GP contact before the epidemic and 46 patients because no eligible controls (i.e. with current high-risk disease) were available for these patients. In all, 119 cases were available for analysis.

**Identification of controls**
In April 1997, using a computerized sampling schedule, we randomly sampled three control patients for every potential case from the database with the remainder of the cohort, matched for age (in the same 5-years age-category) and sex. Controls were not reported as hospitalized or deceased during the epidemic. Of the 357 controls that were sampled from the database for the 119 remaining cases, 12 were excluded because no data were available for these patients. In addition, 149 patients without high-risk disease at baseline, with a

lack of GP contacts or who moved out or died before the epidemic were excluded, because they, retrospectively, were not part of the cohort, which resulted in 196 valid controls.

**Measurements in cases and controls**

Baseline demographic information on age, gender and health insurance (private or National Health Service) was collected by data generated using the influenza prevention module.[7] Further detailed information on potential risk factors was collected retrospectively by review of GP medical records. Presence of concomitant high-risk disease and previous hospitalization resulting from complications related to the high-risk conditions in the 12 months preceding the epidemic was verified by GPs. Use of medical drugs was reported if used chronically for the conditions and the number of GP consultations during the preceding year was counted. Immunization of both cases and controls who complied with the written invitation took place during mass vaccination sessions at the GP's office in November 1996. In the Netherlands, most outpatients receive the vaccine through the GP immunization program.[8] The trivalent sub-unit vaccine composition complied with WHO recommendations and matched well with circulating strains.[12] A person was taken to be a vaccinee for 1996 if the ICPC-code R44.1 (required for reimbursement), was present in the patient record within two months prior to the start of the epidemic.[7]

**Statistical analysis**

Data entry and univariate analysis were performed with use of the commercially available statistical package SPSS for Windows (version 9.0). Distributions of all variables by case and control status were calculated using descriptive statistics. Univariate analysis included *T*-tests for continuous variables and chi-square tests for categorical variables to assess statistically significant differences between cases and controls. Multivariable conditional logistic regression analysis for matched case-control studies with EGRET (Statistics and Epidemiology Research Corporation, Seattle, Washington) was applied to assess independent associations of potential prognostic indicators with the outcome parameter. In the modeling procedure, only those variables were entered in the multivariable model that were associated with the outcome at a *P*-level less than 0.20 in the univariate analysis (8 variables in total). Missing data on an independent variable were considered as absence of the factor. Both stepwise and backward elimination procedures were used to construct the final model. Influenza vaccine status was forced into the final model to assess its potential protectiveness irrespective of statistical significance. As under-use of vaccines is most common in younger populations,[13] we specifically addressed

the relative influence of potential prognostic factors in subgroups of high-risk patients over and under 65 years of age. In a subgroup analysis in age-strata (<65, ≥65 years), the same variables of the overall final model were forced into both separate models. Robustness of the models was assessed by the Hosmer-Lemeshow goodness-of-fit test. Adjusted odds ratios (OR) and their 95% confidence intervals (CI) were calculated. Vaccine effectiveness was calculated as 1 minus the odds ratio (as approximation of the relative risk) in vaccinees times 100 percent.

## Results

Mean age of the patient cohort of 18,163 persons was 62 years (SD 18, range 18-102 years) and 49 percent were male. Based on coded entries, cardiovascular and pulmonary disease appeared present in 36 and 32 percent, respectively, whereas 18% were registered with various codes indicating more than one high-risk condition. Diabetes, renal disease and immune-related disease appeared far less frequent: 12%, 1% and 1%, respectively.

Of the 119 incident cases, 44 (37%) cases had died, 31 (26%) suffered from an exacerbation of underlying pulmonary disease, 22 (18%) from heart failure, eight (7%) from pneumonia, eight (7%) from myocardial infarction, five (4%) from diabetes dysregulation and in 1 the only diagnosis was influenza. Written certification of case diagnosis by a specialist was obtained in 49 (41% of cases). Mean hospital stay was 13 days (95% CI 10-17 days) and appeared equal in those under and over 65 years. Sixteen (16%) were treated at the intensive care unit. Mean age of cases and controls was 70 years (SD 14 years) and 55% was male. The baseline characteristics of cases and controls are summarized in Table 1.

In multivariate analysis, the following factors appeared to be independently associated with the outcome in the total study population (Table 2): previous hospitalization (odds ratio [OR] 1.9; 95% CI 0.9-4.1), ≥5 GP consultations in the preceding year (OR 2.5; 95% CI 1.3-4.8), polypharmacy (OR 1.3; 95% CI 1.1-1.7 per additional drug), presence of COPD (OR 3.5; 95% CI 1.5-8.3), heart failure (OR 3.3; 95% CI 1.0-11.2) or more than one high-risk condition (OR 3.2; 95% CI 1.5-7.2) and NHS insurance (OR 3.7; 95% CI 1.5-8.7). Influenza vaccination in 1996 had a moderate and statistically non-significant protective effect (20% reduction of the outcome parameter) after adjustment for all other prognostic factors in the model.

**Table 1.** Characteristics of cases (n=119) and controls (n=196)

| | Cases | | Controls | |
|---|---|---|---|---|
| **Characteristic*** | **No.** | **%** | **No.** | **%** |
| Age ≥ 65 years | 83 | 70 | 120 | 61 |
| Male | 64 | 54 | 111 | 56 |
| NHS insurance | 103 | 87 | 133 | 68 |
| Medical history | | | | |
| Asthma/other PD | 3 | 2 | 13 | 6 |
| COPD | 24 | 20 | 30 | 15 |
| CHF | 9 | 8 | 7 | 4 |
| Myocardial Infarction | 7 | 6 | 17 | 9 |
| Other CVD | 14 | 12 | 62 | 32 |
| Diabetes | 12 | 10 | 28 | 14 |
| Other HD | - | - | 4 | 2 |
| ≥1 high-risk disease | 50 | 42 | 35 | 18 |
| GP visits | | | | |
| 1-2 | 26 | 22 | 78 | 40 |
| 3-4 | 20 | 17 | 50 | 25 |
| ≥ 5 | 73 | 61 | 68 | 35 |
| Previous hospitalization | 36 | 30 | 19 | 10 |
| No. drugs (mean, SD) | 2.8 | 1.5 | 3.5 | 1.5 |
| Vaccine uptake | | | | |
| 1994 | 72 | 61 | 109 | 56 |
| 1995 | 81 | 68 | 127 | 65 |
| 1996 | 105 | 88 | 174 | 89 |

* PD = pulmonary disease (tuberculosis, pleurisy, lung cancer); COPD = chronic obstructive pulmonary disease; CHF = congestive heart failure; CVD = cardiovascular disease (angina pectoris, chronic ischaemic disease, atrial fibrillation, stroke, paroxysmal tachycardia, cor pulmonalis, valvular heart disase, pulmonary embolism); HD = high-risk disease (renal dysfunction, leukemia, multiple sclerosis, hyperthyreoidy); GP = general practitioner; SD = standard deviation.

Table 2 also shows results of the subgroup of certified cases and their controls. Except for the indicator previous hospitalization and NHS insurance, point estimates of adjusted relative risks are similar or somewhat higher than those assessed in all cases and controls.

**Table 2**. Prognostic factors for influenza-related hospitalization and death: total study population and specialist-confirmed cases and controls are given

| | Total study population (n = 315) | | | Confirmed cases and controls (n = 129) | | |
|---|---|---|---|---|---|---|
| Characteristic | Cases (n=119) No. (%) | Controls (n=196) No. (%) | Adjusted OR (95% CI) | Cases (n=49) No. (%) | Controls (n=80) No. (%) | Adjusted OR (95% CI) |
| NHS insurance* | 103 (87) | 133 (68) | 3.7 (1.5-8.7) | 42 (86) | 55 (69) | 3.0 (0.6-13.6) |
| COPD† | 24 (20) | 30 (15) | 3.5 (1.5-8.3) | 9 (18) | 13 (16) | 5.0 (1.1-23.7) |
| CHF† | 9 (8) | 7 (4) | 3.3 (1.0-11.2) | 5 (10) | 4 (5) | 9.9 (1.3-73.4) |
| > 1 high-risk disease‡ | 50 (42) | 35 (18) | 3.2 (1.5-7.2) | 23 (47) | 13 (16) | 5.6 (1.5-21.1) |
| ≥ 5 GP consultations¶ | 73 (61) | 68 (35) | 2.5 (1.3-4.8) | 31 (63) | 29 (36) | 4.1 (1.2-13.9) |
| Previous hospitalization§ | 36 (30) | 19 (10) | 1.9 (0.9-4.1) | 10 (20) | 7 (9) | 1.0 (0.3-4.1) |
| No. drugs (x, SD) | 2.8 (1.5) | 3.5 (1.5) | 1.3 (1.1-1.7) | 3.4 (1.4) | 2.1 (1.4) | 1.4 (1.0-1.9) |
| Vaccinated in 1996†† | 105 (88) | 174 ( 89) | 0.8 (0.4-2.0) | 41 (84) | 73 (91) | 0.9 (0.2-4.6) |

* versus private insurance;† versus other high-risk disease; ‡ versus one high-risk disease;
¶ versus 1-4 GP consultations; § versus no hospitalization;††versus no vaccination in 1996

When analyzed according to age, most associations appeared stronger in patients aged 18-64 years (Table 3). Much stronger associations were observed for the prognostic factors NHS insurance, presence of COPD and more than one high-risk condition.

## Discussion

Our study showed that routinely obtained clinical information on patients in the community with chronic medical disorders can be used to predict influenza-associated hospitalization and death during epidemics given an influenza vaccination rate in these groups as high as 90%. Moreover, the identified prognostic factors appeared to be even more strongly related to development of serious complications of influenza in those under 65 years of age. These results can facilitate reaching most vulnerable patient groups for additional preventive or therapeutic measures by physicians in both primary and secondary care and

**Table 3**. Prognostic factors for influenza-related hospitalization and death in patients under and over 65 years of age

| | 18-64 years (n =1 12) | | | | | ≥65 years (n = 203) | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Characteristic | Cases (n=36) No. (%) | | Controls (n=76) No. (%) | | Adjusted OR (95% CI) | Cases (n=83) No. (%) | | Controls (n=120) No. (%) | | Adjusted OR (95% CI) |
| NHS insurance* | 31 | (86) | 49 | (65) | 8.8 (1.1-73) | 72 | (87) | 84 | (69) | 3.1 (1.6-8.5) |
| COPD† | 10 | (28) | 14 | (18) | 15.6 (2.1-120) | 14 | (17) | 16 | (16) | 2.1 (0.7-6.1) |
| CHF† | 1 | (3) | - | | - | 8 | (10) | 7 | (5) | 2.6 (0.7-9.4) |
| > 1 high-risk disease‡ | 15 | (42) | 8 | (11) | 24.9 (2.8-223) | 35 | (42) | 27 | (16) | 2.2 (0.9-5.5) |
| ≥ 5 GP consultations¶ | 21 | (58) | 29 | (38) | 1.1 (0.2-5.7) | 52 | (63) | 39 | (36) | 3.0 (1.4-6.7) |
| Previous hospitalization§ | 15 | (42) | 8 | (11) | 6.8 (1.2-39.4) | 21 | (25) | 11 | (9) | 1.5 (0.6-3.8) |
| No. drugs (x, SD) | 3.6 | (1.6) | 2.1 | (1.5) | 1.4 (1.0-2.1) | 3.5 | (1.5) | 2.4 | (1.5) | 1.3 (1.0-1.7) |
| Vaccinated in 1996†† | 32 | (89) | 65 | (86) | 0.7 (0.1-4.7) | 73 | (88) | 110 | (92) | 0.9 (0.3-3.0) |

* versus private insurance;† versus other high-risk disease; ‡ versus one high-risk disease;
¶ versus 1-4 GP consultations; § versus no hospitalization;††versus no vaccination in 1996

such information is important for winter hospital admissions planning. Also, identified factors may be valuable indicators that should be controlled for in case of presence of prognostic dissimilarities among exposed and non-exposed in future non-experimental evaluations of influenza vaccination or anti-influenza agents such as neuraminidase inhibitors.

A limitation of our study is that diagnostic uncertainty in primary care may have induced biased associations. The case-definition used included various acute diseases as diagnosed by GPs. Nichol et al. have stressed that the full range of complications potentially associated with influenza including respiratory, cardiac and diabetes complications should be taken into account when evaluating vaccine effectiveness.[14] It is, however, unlikely that systematic error resulting from diagnostic bias in the study base was present since overall point estimates of associations were similar in the analysis restricted to specialist-confirmed cases with their controls. Although virological confirmation of influenza virus infection was not available for cases, we believe that influenza was directly or indirectly involved in many complications. Limitation of case detection to the weeks in which influenza A and B were highly epidemic according to reported

incidence of influenza-like illness from Dutch sentinel practices, the temporal correlation between case-incidence and influenza-like illness during the surveillance period, and the observation that other viruses like the respiratory syncytial virus may be relatively less prevalent when influenza activity is peaking, support this contention.[12]

Our study lacked adequate power to detect a statistically significant reduction in serious complications resulting from influenza vaccination in this population with very high vaccination rates. Nonetheless, our data indicate that a 10 to 30% reduction of complications may be achieved with the conventional trivalent influenza vaccine. These estimates are in agreement with earlier reports and tend to underestimate the true reduction of complications resulting from absence of virological confirmation.[14-18]

The study domain of our case-control study was limited to patients with current high-risk morbidity. Although an age-based influenza vaccine policy was demonstrated effective and cost-saving,[14] we believe that the impact of additional measures against influenza and its complications can be most effectively increased through reaching the most vulnerable patients with these conditions.

Our study is unique in that we determined prognostic factors in a non-selected outpatient group with a high influenza vaccination rate. Nonetheless, our findings are in accord with results of the few earlier studies that provided information on clinical determinants of potentially influenza-associated disease although different populations were examined and influenza immunization rates were much lower. Ohmit and Monto, for example, estimated similar relative risks in those with pulmonary or cardiac disease as observed in our study, although underlying disease was self-reported by patients and aggregated to large disease-categories.[18] Fleming and colleagues observed increased risks for primary care patients with chronic pulmonary disease, but not for those with cardiac disease.[19] In their study, GP medical records were available for 50% of cases that were originally identified which may have masked the role or some prognostic factors we observed in our study. In elderly and those with cardiac, pulmonary and more than one high-risk disease, Barker et al. observed increased risks of pneumonia and influenza deaths.[20] No information was present, however, on primary-care based prognostic indicators such as GP visits and previous hospitalization. In a large hospital-based study, Glezen and colleagues observed pulmonary disease being the most important prognostic variable for hospitalization due to acute respiratory disease as was cardiac disease for death during influenza epidemics.[21] Furthermore advancing age was associated with higher hospitalization rates. Paul et al. showed influenza-related febrile illness to be more com-

mon among patients with pulmonary disease than others, but in patients with cardiac disease and with previous hospitalization such an increased risk was not observed.[22] In their study, information was collected from clinic charts which may lack valuable information on other primary care-based factors.

Among the non-modifiable prognostic factors that were associated with the case status in our study, few were unexpected. Polypharmacy should be considered an indicator of severe underlying disease. In the elderly Dutch population, two-thirds of persons are insured through the National Health Insurance. NHS insurance status was much more prevalent in cases than controls and is considered an important indicator of lower social economic status of patients. In addition, patients with COPD and those with heart failure appeared to be more at risk than asthmatics or those with other cardiovascular disease including previous myocardial infarction. Most likely, the condition of these specific patient groups is most prone to exacerbations resulting from viral infections. In addition, a high GP visiting rate has been an important prognostic indicator in many community- and primary care-based studies among various disease categories.[14-16,23] In an earlier influenza vaccine cost-effectiveness study among the high-risk segment of patients with chronic lung disease we also found that 90% of hospitalized patients had COPD, heart failure or a high GP visiting rate.[23] Interestingly, the same indicators are of particular importance in adult patients under 65 years. In the elderly, ageing and poorer immunity against viruses are strongly associated with increased risks for morbidity from influenza whereas in younger patients underlying disease might mainly be responsible for development of complications. This finding supports current immunization recommendations.[5,6]

In establishing unbiased estimates of clinical effectiveness of preventive measures and therapy, community-based pragmatic experiments are considered most rigorous.[24] However, scientists face major problems to design such investigations mainly because of ethical issues, sample size limitations and unpredictability of influenza occurrence.[25] Therefore, many non-experimental intervention studies have been carried out.[14-18,21,23,25] More are to be expected among different target groups and effectiveness of other anti-influenza agents as newly developed vaccines as well as prophylactic drugs may be evaluated in the same way. However, since comparability of prognosis among exposed and non-exposed at baseline can be fully achieved by randomization only, non-experimental studies are threatened by confounding bias. Clinical and non-clinical factors may influence vaccine uptake leading to so-called 'confounding by indication'.[24] Consequently, the validity of study results depends on the availability of information to control for inequality in baseline prognosis. Information on

prognostic indicators from our study may be used to more validly assess clinical effectiveness of influenza prevention in non-experimental studies.

In conclusion, since the health-economic consequences of influenza infection are considerable, several identified prognostic clinical indicators of increased risks for serious complications can be used to improve influenza prevention or early treatment among most vulnerable patient groups.

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CHAPTER 3

# A clinical prediction rule for pneumonia and influenza hospitalization and death during influenza epidemics

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**A clinical prediction rule for pneumonia and influenza hospitalization and death during influenza epidemics**

**Background** Uncertainties among providers and patients about a patient's risk for serious influenza associated complications and the potential benefits from vaccination may contribute to unsatisfactory low influenza vaccination rates. In order to quantify risk for serious outcomes during influenza seasons, we developed a clinical prediction rule for the probability of pneumonia or influenza associated hospitalization or death among seniors.
**Methods** We developed the clinical prediction rule using data from linked, administrative databases on 16,280 non-institutionalized and unvaccinated seniors. Validation of the rule was conducted in five unvaccinated and six vaccinated additional cohorts of more than 11,000 elderly members of three managed care organizations. Using logistic regression analysis, the following predictors were selected: age, gender, presence of pulmonary, cardiac and renal disease, dementia/stroke and cancer, number of outpatient visits and hospitalization for pneumonia and influenza in the previous year.
**Results** Reliability of the regression model was good (goodness-of-fit test, p=0.64) and it discriminated well between those with and without the combined end point (area under the receiver-operating curve 0.83, 95% CI 0.81-0.85). Validation revealed moderately lower but acceptable discriminating values between 0.72 and 0.81. The prognostic accuracy of the prediction rule in the derivation cohort was high when a cut-off sum-score ≥50 points, reflecting a predicted probability ≥1.0%, is chosen (subjects with end point vaccinated: 89%, without end point unvaccinated: 51%) while only 50% of seniors would be selected for vaccination. The influenza vaccine reduced hospitalization or death by 43% (95% CI 39% to 47%) in subjects with a high score (≥50 points).
**Conclusions** The prediction rule may be useful to make sure that at risk seniors are vaccinated and to target additional measures for vaccination to those most likely to benefit.

**Key words:** influenza, immunization, elderly, administrative database, epidemiology

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Influenza continues to cause considerable morbidity and mortality worldwide.[1] In the United States, it is estimated that influenza is responsible for hundreds of thousands of hospitalizations,[2] tens of thousands of deaths[3] and billions of dollars in excess costs.[4] Most of the excess morbidity and mortality occurs among the elderly. To reduce these consequences of influenza, recommendations include yearly vaccination of vulnerable patient groups.[5,6]

Although influenza vaccination is effective in reducing morbidity and mortality,[7-10] and cost-saving among the elderly,[11] nearly 40 percent of this

target population fail to receive the vaccine each year.[5] Vaccination rates for high-risk persons under 65 are even lower. Uncertainties among providers and their high risk patients about the risk of serious, influenza related, complications and benefits of vaccination may contribute to these low vaccination rates. Recent data from a survey of Medicare beneficiaries, for example, suggest that lack of awareness of personal risk is among the most common reasons for failing to receive the influenza vaccine.[12]

Another recent issue attracted attention to a higher need for individual risk stratification. In a notice to readers, physicians were urged to identify high-risk persons because a shortfall of the influenza vaccine was expected for the 2000-2001 season.[13] This might happen more often during coming influenza seasons and in case of a pandemic a substantial delay or shortfall of vaccine will likely occur as well in which information on a patient's risk will undoubtedly be of use.[14]

For these reasons a careful risk assessment using an accurate, objective model of prognosis could help physicians assess risks of individual patients and improve the decisions about immunization and additional care. We assessed the prognostic value of clinical information derived from administrative databases of three health plans to develop a prediction rule for the probability of hospitalization for pneumonia and influenza and all-cause death during influenza epidemics among non-institutionalized persons over 65 years of age. We further demonstrated performance of the model when applied to our patients and the consequences of its use in future populations.

## Methods

**Setting**

This study is part of an ongoing collaborative effort between three large managed care organizations from geographically disparate locations across the US to pool data derived from their linked medical databases in order to provide assessments of impact of influenza and the health and economic benefits of vaccination among members of their health care plans. HealthPartners (HP) is a nonprofit health maintenance organization with about 890,000 members in Minnesota and Wisconsin. It offers coverage for 280,000 members through a staff model HMO, while the other members are covered through a network HMO model. Kaiser Permanente Northwest Division (KPNW) provides medical care for nearly 420,000 persons in the Portland, Oregon-Vancouver and Washington regions. Oxford Health Plans (Oxford) provides health benefit

plans to 1.8 million members in New York, New Jersey, Pennsylvania and Connecticut. In all, over 3 million members receive medical care from these health plans. The health plans used protocols specifying the same definitions of co-morbidity and outcomes and obtained all study data, including baseline information, vaccination status and outcomes from their linked, administrative and clinical databases.

**Study subjects**

All members of the three health plans, aged over 65 years as of October 1, 1996 in the first year and October 1, 1997 for the second year, continuously enrolled for 12 or more months prior to October 1 of each year and non-institutionalized were included. A large enrollment period was chosen to ensure valid prognostic information to derive and validate the regression model.[15] Institutionalized patients were excluded because vaccination status was unknown.

**Definitions of potential predictors**

After an extensive literature search, we selected 15 clinical characteristics that possibly could be related to serious clinical outcomes during influenza epidemics. At baseline, the following potential predictors were included: age, gender, and a hospitalization for influenza and pneumonia and number of outpatient visits in the previous year. Underlying disease of eligible subjects was classified into 11 non-mutually exclusive disease categories according to entries of relevant codes in the *International Classification of Diseases, Ninth revision, Clinical Modification* (ICD-9-CM) in outpatient clinic or hospital databases 12 months prior to October 1 of each year: (1) pulmonary disease (ICD-9-CM codes 011, 460, 462, 465-466, 480-511, 512.8, 513-517, 518.3 518.8, 519.9, 714.81), (2) cardiac disease (093, 112.81, 130.3, 391, 393-398, 402, 404, 410-429, 745-746, 747.1-747.49, 759.82, 785.2, 785.3), (3) diabetes/other endocrine disorders (250-251), (4) renal disease (274.1, 403, 580-591, 593.71-593.73, 593.9), (5) immune-deficiency/organ transplants (042, 079, 279, V08, V42) (6) non-hematological and hematological cancer (140-198, 199.1, 200-208), (7) anemia spleen (280-289, 759.0), (8) cirrhosis (571), (9) nutritional deficiencies (254-255, 259.2, 260-269), (10) dementia/stroke (290-4, 331, 340-1, 348, 438), and (11) vasculitis/ rheumatologic diseases (446, 710, 714-714.4, 714.8, 714.89, 714.9).

**Influenza seasons and vaccination**

During the 1996-97 and 1997-98 epidemic, influenza activity was widespread in most US states, exceeding baseline levels for more than 5 consecutive weeks.[16,17] Influenza periods were defined as follows on the basis of Centers of Disease Control (CDC) surveillance data: Year 1, HealthPartners November

22, 1996 through May 24, 1997, Oxford: October 5, 1996 through May 3, 1997. Kaiser: November 22, 1996 through March 22, 1997. Year 2, HealthPartners: December 7, 1997 through March 28, 1998, Oxford: November 23, 1997 through April 4, 1998, Kaiser: December 21, 1997 through March 7, 1998. Vaccination rates varied from 39% to 71% during the years in the different health plans.

**End point**

The combined end point was the occurrence of hospitalization for influenza or, its main complication, pneumonia (ICD-9-CM codes 480-487) or death from all causes during the studied influenza seasons.

**Model development**

To develop the model, we used the data on all eligible study subjects from the HealthPartners database that were enrolled in the first season and who were not vaccinated against influenza (n=16,280). Absence of a characteristic in the medical database was assumed to indicate no presence of the characteristic under study and therefore missing values were absent. Age was classified into the following 5 categories according to exponential increase in risk of outcomes: 65-69, 70-74, 75-79, 80-89, ≥90. Similarly, the number of outpatient visits during the prior 12 months was classified into 4 categories: 0, 1-6, 7-12, ≥13. Descriptive statistics as proportions and means (SD) using SPSS for Windows, version 9.0, (SPSS Inc., Chicago, Illinois, USA) were calculated to describe baseline characteristics in the two comparison groups (with or without end point). The construction of the prognostic model started with a univariate assessment of the prognostic effect of each characteristic separately as given in terms of odds ratio's (OR) and their 95% confidence intervals (95% CI) using logistic regression analysis. In the next stage we used multivariate logistic regression modeling with a backward elimination procedure to select those variables that were related to the outcome with a p-value <0.15 as a criterion for selection. We first used the continuous variables age and number of outpatient visits to ensure that the selection of the corresponding classified variables was independent of the choice of the cut-off values. Forward selection was additionally performed to verify whether any previously deleted potentially relevant characteristic was incorrectly eliminated from the model. Interaction between variables included in the model was assessed to determine deviations from the additivity assumption by including first-order interaction terms in the final model. For each patient we calculated the individual probability of the outcome from the final model (predicted probability).

**Model evaluation**

The reliability of the multivariate logistic regression model derived from the derivation set was determined by the Hosmer-Lemeshow goodness-of-fit statistic.[18] The area under the receiver-operating-curve (ROC) was used to assess the model's discriminative ability.[19] The ROC is a plot of the true-positive rate (sensitivity) and false-positive rate (1-specificity) which is evaluated for each cut-off point of the predicted probability. The area under the ROC can be explained as the probability that the logistic regression model will assign a higher probability of the outcome to a randomly chosen patient with an outcome (hospitalization/death) than to a randomly chosen patient without outcome. An area under the curve (AUC) estimate of 0.5 indicates no discrimination whereas an estimate of 1.0 indicates perfect discrimination. External validation of the model was performed by comparing the AUC values across the other 11 cohorts stratified by immunization status (no/yes), site (1,2,3) and year (1,2).

**Development and applicability of the prediction rule**

The regression coefficients of the derived multivariate model were used to construct the prediction rule.[20,21] The predicted probability of outcome equals $1/\ 1 + e^{-(LP)}$ where the linear predictor (LP) = -6.0906 + 0.4681×age-category + 0.2939×gender + 2.0872×previous P&I hospitalization + 0.3794× outpatient visits-category + 0.6012×lung disease + 0.1952×heart disease + 0.4135×renal disease/transplant + 0.7273×dementia/stroke + 1.5887×cancer. For practical interpretation we have chosen to multiply the regression coefficients by 30 and round them to form the score. All scores indicating the relative influence of the variable on the occurrence of the combined endpoint were added to form a sum-score and classified. For sum-score cut-off points the following test characteristics were calculated: positive predictive value, sensitivity, specificity, proportion of outcomes missed (1.0-sensitivity) and proportion of persons selected.

**Vaccine effectiveness**

To assess whether patients with high or low risk score could benefit from the influenza vaccine, we calculated the vaccine effectiveness for the seniors in both risk groups using logistic regression. In this analysis, the association of vaccination status as main explanatory variable with the dichotomous end point was assessed, independent of other predictors, site and year. Vaccine effectiveness (VE) was determined as 1- OR times 100 percent.[11] Absolute reduction (AR) per 1,000 vaccinees was calculated as the vaccine effectiveness (VE) times the incidence of the end point in non-vaccinees.

## Results

Of the 16,280 study subjects of the derivation cohort, 399 were hospitalized or died during that season (2.5%); 122 (0.7%) were hospitalized for pneumonia or influenza and 287 (1.8%) died from all causes.

**Table 1.** Association of clinical characteristics with hospitalization and death in derivation set (n= 16,280). Percentages are given, unless stated otherwise

| Characteristic | Patients with outcome (n=399) | Patient without outcome (n=15,881) | Univariate Odds ratio (95% CI) | Multivariate Odds ratio* (95% CI) | P-value |
|---|---|---|---|---|---|
| *Demographics* | | | | | |
| Mean age (SD), y | 81 (8) | 75 (8) | 1.8 (1.6-1.9)† | 1.6 (1.4-1.8)† | <0.001 |
| Female | 41 | 38 | 1.2 (1.0-1.4) | 1.3 (1.1-1.7) | 0.008 |
| *Prior health care use* | | | | | |
| Previous P&I hospitalization | 16 | 1 | 22.4 (16.3-30.6) | 8.1 (5.7-11.5) | < 0.001 |
| Mean (SD) no. outpatient visits | 26 (27) | 11 (14) | 2.4 (2.1-2.7)† | 1.5 (1.3-1.8)† | < 0.001 |
| *Co-morbidity‡* | | | | | |
| Heart disease | 50 | 24 | 3.2 (2.6-3.8) | 1.2 (1.0-1.5) | 0.10 |
| Lung disease | 40 | 14 | 4.1 (3.3-5.0) | 1.8 (1.4-2.3) | <0.001 |
| Dementia/stroke | 31 | 9 | 4.6 (3.7-5.8) | 2.1 (1.6-2.7) | <0.001 |
| Renal disease | 13 | 4 | 4.0 (2.9-5.4) | 1.5 (1.1-2.1) | 0.02 |
| Cancer | 12 | 2 | 6.8 (4.9-9.4) | 4.9 (3.4-7.0) | <0.001 |
| Diabetes | 19 | 12 | 1.8 (1.4-2.3) | - | |
| Anemia | 24 | 8 | 3.7 (2.9-4.7) | - | |
| Nutrional def. | 5 | 2 | 3.7 (2.4-5.9) | - | |
| Vasculitis/rheum | 3 | 2 | 1.3 (0.7-1.3) | - | |
| Immunedeficiency | 2 | 1 | 2.0 (1.0-4.0) | - | |
| Cirrhosis | 1 | 0.3 | 3.1 (1.1-8.7) | - | |

-: p-value >0.15

* Likelihood ratio test (LR): p<.001; Hosmer-Lemeshow Goodness-of-fit test: p=0.65

† odds ratio's for the corresponding classified variable are given

‡ see methods section for corresponding ICD-9-CM codes

Mean age was 75 years (SD 8, range 65 to 110 years) and 38% were male. High-risk co-morbid conditions, e.g. cardiopulmonary disease, were present in 47% of subjects.

**Table 2.** Area under the receiver-operating-curve (AUC) and 95% confidence intervals (95% CI) of the clinical prediction rule in validation cohorts by year, immune status and region

| Population | Year 1 | | | Year 2 | | |
|---|---|---|---|---|---|---|
| | N | AUC | 95% CI | N | AUC | 95% CI |
| *Non-immunized* | | | | | | |
| Region A | 16,280 | 0.83 | 0.81-0.85 | 15,492 | 0.72 | 0.69-0.75 |
| Region B | 23,914 | 0.81 | 0.79-0.84 | 39,641 | 0.77 | 0.76-0.79 |
| Region C | 11,775 | 0.80 | 0.77-0.82 | 11,320 | 0.76 | 0.73-0.80 |
| Overall | 51,969 | 0.81 | 0.80-0.82 | 66,453 | 0.76 | 0.75-0.78 |
| *Immunized* | | | | | | |
| Region A | 24,478 | 0.79 | 0.76-0.82 | 25,019 | 0.73 | 0.70-0.76 |
| Region B | 15,193 | 0.73 | 0.68-0.78 | 34,846 | 0.74 | 0.72-0.76 |
| Region C | 31,334 | 0.80 | 0.77-0.82 | 32,136 | 0.75 | 0.73-0.77 |
| Overall | 71,005 | 0.78 | 0.76-0.79 | 92,001 | 0.74 | 0.73-0.76 |

In gray-shade is the derivation cohort (n=16,280).

In univariate analysis, all potential predictors appeared more prevalent in subjects who were hospitalized or died and statistically significant associated with the combined end point, except for a history of immune-deficiency (see Table 1). In seniors with the end point, markedly higher prevalence of previous P&I hospitalization (16% versus 1%), pulmonary disease (40% versus 14%), dementia/stroke (31% versus 9%) and cancer (12% versus 2%) as compared to controls was observed.

Except for the co-morbid conditions diabetes, anemia, nutritional deficiencies, vasculitis/ rheumatological disorders, immune-deficiency and cirrhosis, all other variables independently contributed to the multivariable logistic regression model (table 1). In the modeling procedure, the presence of non-related diseases did not add to the limited prediction model including age, gender, previous P&I hospitalization and number of outpatient visits or predictive value was unacceptably low in the validation cohorts ($p>0.15$). After

**Table 3.** Prediction rule for estimating the probability of hospitalization for pneumonia and influenza and all-cause death

| Characteristic | | Score* |
|---|---|---|
| Age | <70 | 0 |
| | 70-74 | +14 |
| | 75-79 | +28 |
| | 80-89 | +42 |
| | >=90 | +56 |
| Female | | +9 |
| Outpatient visits in last year | | |
| | 0 visits | 0 |
| | 1-6 visits | +11 |
| | 7-12 visits | +22 |
| | >=13 visits | +33 |
| Previous hospitalization for influenza or pneumonia | | +63 |
| Co-morbidity: | | |
| | Lung disease | +18 |
| | Heart disease | +6 |
| | Renal disease or transplantation | +12 |
| | Dementia or stroke | +22 |
| | (Non-)haematological cancer | +48 |

* The sum-score for a given persons can be obtained by summing the scores for each applicable characteristic. The sum-score correlates with the predicted probability through the formula (see methods section).

including first-order interaction terms in the final model, six terms were statistically significant: gender×dementia/stroke, heart disease×cancer, age×heart disease, age×hospitalization, lung disease×hospitalization, dementia/stroke× hospitalization. Although it may be clinically plausible that risks of these combinations is more than the additive risks of each separate variable, we decided not to include them in the final prognostic model for three reasons: (1) these interactions were not observed in earlier studies, (2) they were not statistically significant in the other external cohorts and (3) they did not materially contribute to the discriminative value of the model. Performance of the final model was good (Goodness-of-fit test p=0.65). The model discriminated well between those with outcome (predicted probability 10%±1%) and those without outcome (0.2%±0.4%). The AUC was 0.83 (95%

**Table 4.** Test characteristics of sum-score cut-off points in derivation cohort (n=16,280)

| Sum-score Category | No. (%) | OP (%) | RR | Cut-off point | PPV (%) | SE (%) | SP (%) | OM (%) | Selection (%) |
|---|---|---|---|---|---|---|---|---|---|
| ≥0-<10 | 519 (3.2) | 0.2 | 1.0 | 0 | 2.5 | 100 | 0 | 0 | 100 |
| ≥10-<20 | 1153 (7.1) | 0.4 | 2.0 | 10 | 2.5 | 99.7 | 3.3 | 0.3 | 96.8 |
| ≥20-<30 | 2552 (15.7) | 0.2 | 1.0 | 20 | 2.7 | 98.4 | 10.5 | 1.6 | 89.7 |
| ≥30-<40 | 2371 (14.6) | 0.5 | 2.5 | 30 | 3.2 | 96.9 | 26.5 | 3.1 | 74.0 |
| ≥40-<50 | 1579 (9.7) | 1.1 | 5.5 | 40 | 3.9 | 93.6 | 41.3 | 6.3 | 59.4 |
| ≥50-<60 | 2128 (13.1) | 1.2 | 6.0 | 50 | 4.4 | 89.2 | 51.1 | 10.8 | 49.7 |
| ≥60-<70 | 1787 (11.0) | 2.0 | 10.0 | 60 | 5.5 | 82.8 | 64.3 | 17.0 | 36.6 |
| ≥70-<80 | 1329 (8.2) | 2.5 | 12.5 | 70 | 7.1 | 74.0 | 75.3 | 25.8 | 25.6 |
| ≥80-<90 | 938 (5.8) | 4.2 | 21.0 | 80 | 9.2 | 65.7 | 83.5 | 34.1 | 17.4 |
| ≥90-<100 | 700 (4.3) | 5.1 | 25.5 | 90 | 11.6 | 44.1 | 89.2 | 43.9 | 11.6 |
| ≥100 | 1224 (7.4) | 15.4 | 77.0 | 100 | 15.4 | 46.9 | 93.4 | 52.9 | 7.4 |

OP: observed probability of outcome, RR: relative risk (<10 points is reference), PPV: positive predictive value, SE: sensitivity, SP: specificity, OM: outcomes missed

CI 0.81-0.85). AUC estimates were moderately lower, but acceptable across the validation cohorts (see table 2, range 0.72 to 0.81). The average discriminative power was approximately 0.05 points lower in the second as compared to the first season and 0.03 points lower in the immunized as compared to the non-immunized persons.

The prediction rule was derived from the final multivariate model in which a score was assigned to the presence or level of each variable (table 3). A sum-score for each patient, reflecting the probability of reaching an end point, was calculated by adding the scores of relevant characteristics. For instance, the sum-score for a 66-year old female patient with Hodgkin's disease who visited the outpatient clinic 7 times in the previous year and is recently diagnosed with asthma is 97 (9 + 48 + 22 +18) which is a 25.5 times higher risk than the lowest risk category (see also table 4).

The prediction rule can be used to identify those at highest risk for serious influenza associated complications and those therefore most likely to benefit from vaccination. Using the derivation cohort, for each cut-off level of the

**Table 5.** Practical implication of using a cut-off score (≥50) in validation cohorts by year, immunization status, and region. Percentages are given

| Cohorts | Year 1 | | | | | Year 2 | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | OP | SE | OM | SP | RE | OP | SE | OM | SP | RE |
| *Non-immunized* | | | | | | | | | | |
| Region A* | 4.4 | 89 | 11 | 51 | 50 | 2.3 | 81 | 19 | 50 | 50 |
| Region B | 3.7 | 81 | 19 | 65 | 64 | 3.9 | 83 | 17 | 54 | 53 |
| Region C | 5.5 | 72 | 28 | 70 | 69 | 3.0 | 83 | 17 | 56 | 56 |
| Overall | 4.3 | 82 | 18 | 62 | 61 | 3.3 | 83 | 17 | 54 | 53 |
| *Immunized* | | | | | | | | | | |
| Region A | 2.0 | 87 | 13 | 47 | 46 | 1.7 | 83 | 17 | 43 | 43 |
| Region B | 1.4 | 80 | 20 | 49 | 48 | 2.3 | 90 | 10 | 36 | 35 |
| Region C | 3.1 | 78 | 22 | 64 | 64 | 2.0 | 87 | 13 | 44 | 44 |
| Overall | 2.2 | 81 | 19 | 55 | 54 | 2.1 | 88 | 12 | 41 | 40 |

OP: observed probability, SE: sensitivity, OM: outcomes missed, SP: specificity, RE: reduction of the target population

* In gray-shade is the derivation cohort (n=16,280).

sum-score we calculated test characteristics (see table 4). A cut-off score of ≥50 had a sensitivity of 89% (1 out of 10 outcomes is missed) while the number of seniors selected would be halved. Patients with low risk assignment (score<50) had an observed average probability of 0.5%, those with high risk (≥50) had an average probability of 4.0%. With increasing cut-off level, the proportion of non-selected persons would increase, but the proportion of outcomes missed increases accordingly. Since the benefits of the cut-off value of ≥50 outweighed the risk of missing disease in the derivation cohort, we showed the practical consequences of this cut-off value in the different validation cohorts (table 5). On average, the sensitivity was high (82% to 83% in the non-immunized, 81% to 88% in the immunized) whereas the reductions of selected persons would range from 40% to 61%. When analyzing the test characteristics for both subsidiary end points separately, results were similar (not in table). Finally, influenza vaccination reduced any hospitalization or death by 43% (95% CI 39% to 47%) in persons with a score ≥50 and 33% (95% CI 24% to 45%) in those <50 points. The absolute reduction resulting from the vaccine in the high-risk segment of the population would be 16 per 1,000 vaccinated persons. In other words, only 67 persons have to be vaccinated to save one end point from happening.

## Discussion

This study is unique in that we were able to derive and validate a prediction rule with acceptable reliability, discriminating ability and generalizibility using data on large-sized cohorts of seniors from three geographically disparate located health plans across the US. In comparison with previous prognostic studies,[7-10,22-26] our prediction rule has distinctive strengths. First, we developed a 9-factor prognostic scoring system in non-selected persons using information on predictors that can be readily assessed by both patients and health care providers at any time. Second, patients can be easily assigned to high or low risk category enabling providers to balance costs and benefits of health care. Third, the reliability, accuracy and generalizibility of the rule are supported by derivation in 16,280 seniors and validation in 11 large-sized external cohorts representing other areas across the United States, different epidemic season and immunization status.

The predictors incorporated in our prediction rule have been established in earlier epidemiological studies.[7-10,22-26] Age is a strong predictor for both respiratory infections, its main complication pneumonia and associated death.[27] Males also have been found to be at higher risk than females for influenza infections.[27] Patients with cardiac disease, especially congestive heart failure, are prone to exacerbations of underlying systemic disorders.[28] In addition, the disseminating potential of influenza infection in the lungs of patients with chronic respiratory disease is well known.[29] Patients with renal transplants[30] and cancer patients receive immune-suppressive medication which put them at risk for infections.[31] Also, previous hospitalization for pneumonia or influenza has been reported previously as a risk factor.[32] Relatively little is known, however, about the risk of elderly with dementia or stroke. Our results indicate that there is substantial risk for these persons of dying or being hospitalized during an influenza epidemic.

Diabetes was not independently associated with a higher risk of P&I hospitalization or death in both derivation and validation cohorts. In the modeling procedure, similar information needed for risk assessment was acquired through other predictors as age, gender and previous health care use. It appeared that two-thirds of diabetics had a score ≥50 points and therefore the disease may be seen as an indicator for high influenza risk which is in accordance with other studies.[33]

To our knowledge, this is the first study to demonstrate that risks are not materially modified by changing epidemics or immunization status. We believe

therefore that results are applicable to future epidemic seasons. Furthermore, our prediction rule may be used in non-vaccinated persons, especially those who have high scores, to efficiently target them for influenza vaccination and other appropriate medical care whereas in vaccinated persons with high scores, risk assignment based on the rule help practitioners direct medical care and for those with low scores avoid unnecessary additional diagnostic, therapeutic or preventive measures.

A score ≥50 points represented a high risk with an average expecting occurrence rate of P&I hospitalization or mortality of 4%. In the derivation cohort, relatively lower numbers of persons were observed with higher cut-off values while the numbers of outcomes missed increased substantially. Although we acknowledge that the proportion of outcomes missed decreases with a lower cut-off score, we feel that using the cut-off level of 50 points was acceptable in all validation cohorts whereas the numbers to select for care were reduced to between 40% and 60% on average. From the scoring formula some patient profiles with high risk can easily be identified on the basis of routine clinical information: e.g. everyone who has had a previous hospitalization for pneumonia or influenza or a history of cancer and who is aged over 90 years, and all elderly aged over 80 years with at least one of the high-risk co-morbid conditions. Since we demonstrated that influenza vaccination reduced P&I hospitalization or death by 43 percent in persons with a score ≥50 points, no opportunities should be missed to vaccinate these persons against influenza and pneumonia.

For the development of the clinical prediction rule, we studied only persons aged 65 years and older. The majority of excess deaths and many, if not most, of the excess hospitalizations for influenza associated complications occur in this group. However, for many years, persons with high-risk conditions under age 65 have also been included among the high risk groups targeted for vaccination, and for the 2000-2001 season, the ACIP lowered its age-based recommendations for annual vaccination down to 50 years.[34] How our prediction rule might apply to these other high-risk groups remains to be seen.

We used pneumonia and influenza hospitalizations and deaths from all causes as the end points for the prediction rule. These outcomes are highly correlated and have traditionally been among the main measures used to assess and define the magnitude and impact of influenza epidemics.[1] However, influenza may also be responsible for a wide range of other complications including exacerbations of underlying medical conditions leading to increased outpatient and inpatient health care use.[11] It is not clear how the results of our model might apply to these other outcomes.

In conclusion, we derived and validated a prediction rule for quantifying the probability of P&I hospitalization or death with acceptable reliability, discriminating ability and generalizibility. In addition to the recommendation to routinely immunize all persons over 50 years of age against influenza, our prediction rule may help practitioners to target efficiently additional efforts to those who need preventive and therapeutic measures most.

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# Part II

## Clinical effectiveness of influenza vaccination

CHAPTER 4

# Confounding by indication in non-experimental evaluation of vaccine effectiveness: the example of influenza vaccination

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**Confounding by indication in non-experimental evaluation of vaccine effectiveness: the example of influenza vaccination**

Randomized allocation of vaccine or placebo is the preferred method to assess the effects of the vaccine on clinical outcomes relevant to the individual patient. In the absence of phase 3 trials using clinical endpoints, alternative non-experimental designs to evaluate vaccine effects or safety are often used. The application of these latter designs may, however, lead to invalid estimates of vaccine effectiveness or safety. Since patients with poor prognosis are more likely to be immunized, selection for vaccination is confounded by patient factors that are also related to clinical endpoints. This paper describes several design and analytical methods aimed at limiting or preventing this confounding by indication in non-experimental studies. In short, comparison of study groups with similar prognosis, restriction of the study population and statistical adjustment for dissimilarities in prognosis are important tools and should be considered. Only if the investigator is able to show that confounding by indication is sufficiently controlled for, results of a non-experimental study may be of use to direct an evidence-based vaccine policy.

**Key-words:** influenza, vaccine, effectiveness, confounding, methods, observational studies

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The health economic impact of influenza epidemics is considerable.[1-3] In most western countries, the use of inactivated influenza vaccines by vulnerable patient groups is advocated to prevent complications.[4] However, uptake of the vaccine remains low, especially in those who need it most.[4-6] Disbelief in the vaccine 's effects on clinical outcomes relevant to the individual patient may be one of the major reasons for disappointing immunization rates.[3,4,6-8]

**Effectiveness of influenza vaccination: randomized controlled trials**

The clinical effects of influenza vaccines such as reduction of major symptomatic events or death should preferably be studied in phase 3 randomized controlled trials (RCT).[9] Provided that the sample size is large enough, randomized assignment of patients to vaccine or placebo enables valid assessment of vaccine effects through comparing the occurrence of outcomes in both patient groups with similar prognosis. Such trials can be conducted among various segments of the patient population and may give insight into positive as well as negative clinical consequences of immunization in daily practice. Results of large enough trials in which the primary endpoint is a clinical outcome rather than a surrogate endpoint (e.g. immune response) provide

crucial information on the true impact of these preventive measures and are best suited to guide health care decisions.[10,11]

However, scientists face many obstacles when planning a RCT for clinical evaluation of influenza vaccines. First and foremost, as the incidence of influenza-related complications or adverse effects is low these trials would entail great expense because large numbers of patients are required.[1,12] Second, several influenza seasons may need to be observed as the virulence of circulating influenza viral types is highly variable and unpredictable.[1,6,13] Finally, once the vaccine has been licensed ethical concerns may be raised to further evaluate its effectiveness in placebo-controlled studies, especially when persons at high risk for complications are involved. Because of these limitations, post-licensing or phase 4 studies evaluating the vaccine's clinical effectiveness or safety usually use a non-experimental approach, notably a case-control or cohort design.[9] The vaccine's effectiveness is interpreted as the percentage reduction in risk of influenza-associated complications attributable to vaccination, given in percent by 1-RR in cohort studies or 1-OR in case-control studies.[3] The main difference between experimental and non-experimental designs lies in the absence of random allocation of the intervention, e.g. vaccination, by the investigator.

**Effectiveness of influenza vaccination: non-experimental studies**

One of the major problems encountered in non-experimental evaluation of intended drug effects is the 'natural' presence of incomparability of prognosis among subjects receiving the drug and those who do not.[14] In non-experimental influenza vaccine studies, the vaccine group typically comprises patients with more severe disease or (perceived) higher risk, either as a result of self-selection or physician preference, than the non-vaccinated (control) group.[15,16] In contrast, those with a contra-indication for the intervention will usually be found in the control group only. Thus, selection of exposure is confounded with patient factors, both clinical and non-clinical, that are also related to (detection of) the outcome. This phenomenon may equally apply to qualitative (absence/presence) as well as quantitative (dosing schedule) aspects of exposure and is usually referred to as 'confounding by (contra-)indication' or 'channeling'.[14,17,18] Crude, unadjusted, results of non-experiments may therefore lead to invalid inference regarding influenza vaccine effectiveness and potential side effects, i.e. underestimation of both beneficial and adverse effects in most circumstances. The obligation of the investigator is to design and analyze the study in such a way that reduction or removal of this type of bias can be achieved.

**Prevention of confounding by indication: study design issues**

Preventing or limiting confounding by indication can be achieved in the design and data-analytic phase of case-control and cohort studies (see also Table 1). In designing a non-experimental study of vaccine effectiveness, valid inferences on preventive effects can be drawn in those situations in which patient groups are compared who have similar indications but have undergone different interventions. These designs could be viewed as 'natural experiments'. Hypothetically, patients receiving the influenza vaccine because their general practitioner (GP) believes in it and is able to organize the intervention program (intervention group) could be compared with a group of patients listed with a GP who does not immunize his patients against influenza (control group). Such comparison groups may however be difficult to identify in one health care system. Another, less preferred, design option constitutes an ecological study in which vaccine effects among patients residing in different areas are compared. Similarity of ecological comparison groups highly depends on distribution of patient characteristics in different areas. In this respect, a design in which the incidence of influenza-associated complications of a historical control group of patients before the introduction of the influenza vaccine is compared with the incidence of such complications in patients after its introduction (intervention group) in one area may be a better option. Such a design, however, risks the incomparability of influenza seasons.

**Table 1.** Methods to reduce confounding by indication

| **Design methods** |
|---|
| • Comparison of groups with similar prognosis (e.g. 'natural experiment' or use of historical controls) |
| • Restriction or stratification of study population (e.g. age-strata, gender, current/inactive disease) |
| • Individual matching of exposed and non-exposed into main prognostic strata ('quasi-experiment') |
| **Statistical methods** |
| • Statistical control of confounding factors in multivariable regression model |
| • Subclassification of patients on levels of the propensity score |
| • Pseudo-randomization on levels of instrumental variables |

Alternatively, the study domain could be restricted to patients with a more or less similar prognosis such as institutionalized elderly patients.[19] Strict admission criteria could however limit the generalizibility and applicability of results to other segments of the population, while incomparability of comparison groups and residual confounding may persist. Stratification of the study population on levels of important confounding variables, like for example age, and within stratum comparisons also enhances internal validity.[20]

Another option consists of individual pair-matching of vaccinated and non-vaccinated subjects within strata of important prognostic variables sometimes referred as 'quasi-experiment'. This technique was used in a non-experimental evaluation of the effects of placement of ventilation tubes and proved to reduce confounding bias.[21] The design of a quasi-experiment is, however, costly as it requires sufficiently large numbers of patients within each stratum. Except for restriction and stratification, to our knowledge none of the other design options mentioned above has been applied in non-experimental evaluation of currently used influenza vaccines.

**Prevention of confounding by indication: data analytical issues**

Independent of the study design, statistical adjustment for dissimilarities in prognostic factors between the patient groups receiving and not receiving the vaccine can be applied to enhance validity.[1,3,22-24] A prerequisite is that valid and precise data are obtained through the design used to estimate the patient's prognosis without too many missing data. In other words, to optimize statistical adjustment, the prognosis of each patient should be measured by as many valid indicators as possible to allow adjustments afterwards. In primary care, for example, the presence of current disease as indicated by presence of GP consultations in the year preceding the study, also referred as 'active patient', is essential to allow valid adjustment of potential confounding. In the ideal situation in which all prognostic patient features can be measured, the exact degree of bias can be quantified and used to draw valid conclusions from the data. In practice, this is usually impossible due to cost restrictions and difficulty, and in that case residual confounding or hidden bias can not be ruled out. However, although in many non-experimental studies residual confounding may be present, it can be shown that there are limits to the extent of mathematical explanation by this unmeasured confounding. Its putative effects mainly depend on the expected prevalence of the unobserved variable(s), and its associations with vaccination and outcome. Investigators should therefore always reflect on the potential magnitude of the impact of such bias on the effectiveness estimate for example by using sensitivity analysis.[16,26]

In general, three main methods for statistical adjustments can be applied: (1) statistical control of confounding variables in a multivariable regression model;[14,18] (2) sub-classifying or matching patients on levels of a so-called 'propensity score' [16,25-27] and (3) the use of an instrumental variable to enable statistical pseudo randomization and to account for any residual confounding.[28]

The first option is commonly used and comprises several steps: identification of confounders in the data-set, univariate stratification of exposure groups on levels of the confounder to estimate the vaccine effectiveness estimate adjusted for this single variable (e.g. age) and multivariable control including confounding variables that collectively influence the estimated relationship between exposure and outcome in the modeling procedure.

A method to optimize statistical adjustment for confounding by indication in non-experimental studies, notably when the number of prognostic variables is large, has been proposed by Rubin and Rosenbaum. They introduced the 'propensity score' method.[16,25-27] This score is the conditional probability of exposure to a treatment given a set of observed variables that may influence the decision to vaccinate. The propensity score can be derived from a multivariable logistic regression analysis in which those variables that are statistically significant associated with exposure (e.g. vaccination) are included. Obviously, the outcome variable should not be included as a co-variate. A higher score indicates a higher probability of receiving the vaccine. Sub-classification of subjects on levels of this single variable or including this variable as a single co-variate in a multivariable regression model tends to balance all of the observed variables, but not the unobserved.[16,25,27] The use of this score and matched sampling will also implicitly incorporate any interactions among confounders. Thus, this technique enables the investigator to assess the association of vaccination with specific outcomes in patients with a more or less equal probability of receiving the vaccine. Discriminant matching for multivariate normal co-variates as described by Cochran[29] and the use of a 'confounder score' as proposed by Miettinen are related techniques.[30]

To overcome the potential lack of balance on unobserved prognostic indicators (e.g. health behavior), the instrumental variable method has been suggested. This technique originates from the field of econometrics and has so far not been extensively used in medical research. In short, patients are subdivided according to levels of a co-variate that is associated with the exposure, but not associated with the outcome. This pseudo-randomization may lead to equal distribution of health characteristics in both non-exposed and exposed people and thus prevent potential confounding. For example, McClellan et al. calculated the

distance to the hospital on the basis of zip-codes and divided patients into those living within a small area around the hospital and those outside that area in a study on cardiovascular procedures.[28] Distance to the hospital did fulfill the criteria for instrumental variables. Heart catheterization was more prevalent in the inner circle than the outer circle, and mortality rates were similar. This was in contrast with their prior finding using conventional control for confounding in which mortality rates appeared higher in patients who underwent the surgical procedure. Since the validity of this latter method should be evaluated in other medical studies and instrumental variables may be hard to identify, we will not further elaborate on this statistical procedure.

The presence of confounding by indication in non-experimental evaluation of influenza vaccination and some of the above-mentioned tools to reduce its impact are discussed in more detail on the basis of data derived from a recent study by our group.

**An example: Influenza vaccine effectiveness in adult patients with pulmonary disease**

We examined the effect of influenza vaccine on the incidence of influenza-associated complications in 1,696 adult patients with chronic obstructive pulmonary disease (COPD) or asthma during the 1995/96 influenza A epidemic.[31] The study was a one-season prospective cohort study using the medical database of the Utrecht General Practitioners Network. GP patient records were reviewed for all study subjects. As a first design approach to limit confounding by indication, vaccinated and non-vaccinated patients with pulmonary disease were compared rather than vaccinated patients and controls from the community. The study population was restricted to those with an indication for vaccination according to the guidelines of the Dutch Health Council. In table 2 we give crude and adjusted effectiveness estimates using the conventional control of confounding by multivariable logistic regression analysis. In spite of restriction of the study population, crude results appear to suggest that the vaccine is ineffective and may even lead to complications (odds ratio (OR) 1.14). However, further statistical adjustments notably for age, disease and GP visits resulted in striking changes of the effectiveness estimate to a relative risk of 0.76 suggesting an overall vaccine effectiveness of 24 percent in this population —a relative parameter change of 33 percent. Addition of other co-variates in the final model did not substantially change the vaccine effectiveness estimate.

**Table 2.** Crude and adjusted odds ratio's for an acute episode of low respiratory tract or cardiac disease or death during an influenza epidemic in vaccinees and non-vaccinees

| Study population and analysis | Adjusted for: | Odds ratio (95% CI) |
|---|---|---|
| Adult patients (18-102 y, n=1696) Conventional control: MLR* | Crude value: | 1.14 (0.84-1.55) |
| | + age (in years) | 0.87 (0.64-1.20) |
| | + disease (asthma/COPD) | 0.82 (0.59-1.13) |
| | + GP visits (in number) | 0.76 (0.54-1.05) |
| | + remaining factors | 0.76 (0.54-1.06) |
| Elderly patients (65-102 y, n=630) Conventional control: MLR* | Crude value: | 0.57 (0.35-0.93) |
| | + age (in years) | 0.56 (0.35-0.92) |
| | + disease (asthma/COPD) | 0.53 (0.32-0.87) |
| | + GP visits (in number) | 0.50 (0.30-0.83) |
| | + remaining factors | 0.50 (0.29-0.83) |
| Younger patients (18-64 y, n=1066) Conventional control: MLR* | Crude value: | 1.27 (0.84-1.94) |
| | + age (in years) | 1.11 (0.73-1.70) |
| | + disease (asthma/COPD) | 1.08 (0.70-1.66) |
| | + GP visits (in number) | 0.94 (0.61-1.47) |
| | + remaining factors | 0.94 (0.60-1.45) |
| Quasi-experiment (18-64 y, n=676) Conventional control: MCLR** | Matched crude value: | 0.90 (0.53-1.52) |
| | + age/ disease/GP visits/ remaining factors | 0.89 (0.52-1.54) |
| Younger patients (18-64 y, n=1066) Propensity score + MCLR** | Matched crude value: | 0.87 (0.56-1.35) |
| | + age/ disease/GP visits/ remaining factors | 0.86 (0.55-1.35) |

* MLR: Multivariable logistic regression analysis;
** MCLR: Multivariable conditional logistic regression

Most probably the adjustments were still incomplete. More precise measurements of disease severity such as pulmonary function, atopy or hyper-reactivity were not available. Therefore, a second approach to limit confounding consisted of subdividing the whole study population into two age-strata (≥65 years, 18-64 years) in which prognosis of vaccinees and non-vaccinees within each age-stratum is less deviant (see also table 2). Apart from issues of modification of the effects of the vaccine by age, which is beyond the scope of this article, with this approach, statistical adjustments for the same confounding factors resulted in smaller relative parameter changes of 12 and 26 percent, respectively, in both age-categories. This suggests that stratification or age-restriction may further reduce residual confounding. Still, inferences on the two age subgroups should be made with caution. In the elderly, a substantial and statistically significant reduction in the outcome rate was observed even without controlling for confounding (OR 0.57, 95% confidence interval [CI] 0.35-0.93). Addition of prognostic factors into the multivariate model led to a further increase in the estimate of vaccine effectiveness indicating some residual confounding after stratification. However, in the working-age adults the crude odds ratio was well above 1.0 and despite adjustment for the available prognostic indicators we could not demonstrate a significant reduction (OR 0.94, 95% CI 0.60-1.45). This suggests that results of restricted populations are not necessarily applicable to other segments, in this case younger patients. Because Neuzil and colleagues showed considerable impact of influenza in a younger group of women[6] and we have shown that in the Netherlands the current influenza target group comprises at least 40 percent of high-risk persons under 65 years of age,[32] we further examined potential confounding in this particular age-group.

As a third approach to limit potential confounding by indication in the original design, we used the data of this younger age group (18-64 years) in a 'quasi-experiment'. First, we identified the three main prognostic factors: age (5-years age-category), underlying pulmonary disease (asthma or COPD) and GP visiting rate (0, 1-2, and ≥3 visits). Next, we classified each subject, vaccinated or non-vaccinated, into one of the 54 combinations of these factors. Within each stratum we then randomly sampled from either the vaccinated or the non-vaccinated group as many patients as were available in the comparison group with the lowest number of subjects. For example, if 5 vaccinated and 2 non-vaccinated patients were between 20 and 24 years old, had asthma and consulted the GP 5 times in the preceding year, we sampled 2 patients at random from the exposed group to form a stratum matched group. In all, 390 patients (37%) were excluded from the original study population (n=1066) and 676 patients were available for the quasi-experiment. After this matching

procedure it appeared that the vaccine reduced the occurrence of outcomes by 11 percent, after adjustments for the main confounders and remaining covariates (i.e. health insurance, gender), but the estimate was not statistically significant (see table 2). Only minor changes were observed after statistical adjustment, suggesting that confounding by differences in the known prognostic factors was largely removed. A major limitation may prohibit the use of the above-mentioned 'quasi experiment'. Pair-matching is time-consuming and can considerably reduce the power of the study as numbers of matched patients in separate strata become small. In our example 37% of the initial study population had to be excluded. To avoid these issues, we finally applied analytical control of confounding by using the 'propensity score'.

In our example, we used the 1066 patients aged between 18 and 64 years to calculate the probability score of being vaccinated. Our final multivariable logistic regression model with the dependent variable vaccination included age, underlying disease, number of GP visits, gender and health insurance. We then categorized the propensity score into quintiles and matched vaccinees and non-vaccinees on levels of the probability to be vaccinated. In the multivariable conditional logistic regression analysis we matched on the categorized levels of the score and calculated crude and adjusted odds ratio's of vaccination for the outcome. The overall adjusted odds ratio of 0.86 appears to suggest a 14% reduction of complications resulting from the vaccine. The finding of the 'quasi-experiment' in which stratum-matched pairs of vaccinees and non-vaccinees were compared was validated by this statistical method. As was expected, 95% confidence intervals were smaller, but point estimates were nearly the same. The latter techniques changed the effectiveness estimate from a crude estimate of –27% in the original design to 11% and 14% using the 'quasi-experiment' and 'propensity score', respectively; relative parameter changes of more than 30%. In addition, the propensity score method resulted in slightly smaller 95% confidence intervals than the conventional adjustment. Although our study lacked adequate power to demonstrate a statistically significant reduction of outcomes resulting from the vaccine, the adjusted effectiveness point estimates are compatible with a statistically significant 11% reduction of outpatient visits for respiratory disease in elderly lung patients as observed by Nichol and colleagues.[33]

## Conclusion

Randomized allocation of vaccine or placebo is the preferred method to assess the effects of the vaccine on clinical outcomes relevant to the individual patient. In the absence of phase 3 trials using clinical endpoints, alternative non-experimental designs to evaluate vaccine effects or safety are often used. The application of these latter designs may, however, lead to invalid estimates of vaccine effectiveness or safety. Since patients with poor prognosis are more likely to be immunized, selection for vaccination is confounded by patient factors that are also related to clinical endpoints. This paper describes several design and analytical methods aimed at limiting or preventing this confounding by indication in non-experimental studies. In short, comparison of study groups with similar prognosis, restriction of the study population and statistical adjustment for dissimilarities in prognosis are important tools and should be considered. Only if the investigator is able to show that confounding by indication is sufficiently controlled for, results of a non-experimental study may be of use to direct an evidence-based vaccine policy.

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